

## **Remarks**

### **Claims**

Claims 2 and 6-8 are cancelled.

Claims 1, 3-4 and 13 are amended. Support for the amendments can be found, for example, in the original claims, page 7, first para., and page 8, para. 3, of the PCT Publication.

No new matter is added. The foregoing amendments and cancellations are made solely to advance prosecution, without acquiescence to any rejection or disclaimer of subject matter removed by amendment, and reserving all rights to pursue such subject matter in continuing or divisional applications claiming the same right of priority as the present application.

### **Response to §103(a) Rejection**

The Examiner rejected previous claims 1-19 under 35 USC § 103(a) and argued that the claims were unpatentable over Lohning et al. (US20020034733) in view of Burger et al. (Appl. Microbiol. Biotechnol. (1999) 52:345-353). The Examiner stated that Lohning et al. fails to disclose a tricistronic vector, but that Burger et al. makes up for this deficiency by teaching a tricistronic vector to achieve stable expression.

The present claims are directed to a library of tricistronic display vectors comprising a regulatable promoter, a nucleic acid encoding a phage coat protein or fragment thereof, nucleic acids encoding immunoglobulin polypeptides, and nucleic acids encoding associating agents which comprise a cysteine residue, wherein upon expression the phage coat protein and an Ig polypeptide associate via their respective associating agents and the Ig polypeptides self-associate. Applicant respectfully asserts that the present claims are non-obvious over Lohning et al. in view of Burger et al.

In order to present a *prima facie* case of non-obviousness, the Examiner must articulate one of the KSR v. Teleflex rationales outlined in MPEP 2143, or find that the teaching-suggestion-motivation (“TSM”) test outlined in MPEP 2143.01 is satisfied, and/or find that a reasonable expectation of success existed to combine the prior art under MPEP 2143.02. MPEP §2143 states that for a *prima facie* case of obviousness to be met, three criteria are required: 1) a suggestion or motivation to modify or combine the reference teachings; 2) a reasonable expectation of success; and 3) the combination of the references must suggest all of the claim limitations. It was made clear in KSR v. Teleflex that the TSM/RES test is still an appropriate framework for non-obviousness analysis.

The Examiner argues that it would have been obvious to use the tricistronic vector of Burger et al. to express the genes disclosed in Lohning et al. as one would have been motivated to do so by the disclosure of Burger et al. of the usefulness of such vectors for obtaining stable expression of three gene products and based upon the high level of skill in the art there would have been a reasonable expectation of success.

Applicant respectfully disagrees.

First, there exists no suggestion or motivation in either reference to combine their teachings. MPEP§2143.01 states that there are three possible sources for a motivation to combine references, including the nature of the problem to be solved, the teaching of the prior art and the knowledge of persons of ordinary skill in the art. The nature of the problem to be solved in Burger et al., versus Lohning et al. and the present application are very different. Burger et al. describes a vector for use in stable cell line production, whereas, Lohning et al. and the present application describe a phage display application. A major difference between the two approaches is that Burger et al. starts with a known protein construct, the mAb425 fusion (one specific antibody sequence), and the output is the same, a single antibody sequence expressed in eukaryotic CHO cells. The problem to be solved is the identification, through trial and error, of a cell line that will express the single antibody fusion with a certain level of production and quantity over time. Whereas, in Lohning et al. and the present invention, the library of vector(s) is used to display billions of different antibody fragments (having unique sequences), which are expressed in prokaryotic cells. The problem to be solved in Lohning et al. was the development of an alternative means of displaying a library of proteins on phage, i.e. Cys Display ®. Because the nature of the problem to be solved in Burger et al. and Lohning et al. are so different, absent some express suggestion or teaching within the references, one of skill in the art would not have been motivated to combine the references. In addition, the problem to be solved by the present application is the provision of a library of display vectors that assures that all three protein products, i.e. the immunoglobulin polypeptides and phage coat protein, are expressed in a balanced way, subsequently associate, and are displayed on each of the billion or so phages without the use of a selection marker, for example, pac. Prior to the present invention, a two vector system was used in phage display, as shown in Lohning et al., where there was no way of determining if all three protein products were present in each phage, as the use of a selection protocol was impossible. The innovation of the single, tri-cistronic vector for use in phage display disclosed in the present application solved this significant problem.

Regarding the knowledge of persons of ordinary skill in the art, Examiner has provided no evidence of what was known to one of skill in the art at the time of the present application, therefore, no suggestion or motivation to combine the references can be found in the knowledge of persons of ordinary skill in the art.

Finally, the references themselves, which represent the teachings of the prior art, provide no suggestion or motivation to combine the references.

In conclusion, there is no suggestion or motivation to combine the teachings of Lohning et al and Burger et al., therefore, Applicant respectfully requests the Examiner to withdraw the rejection.

As an analogous example, in *In Re Rouffet*, 149 F.3d 1350 (Fed. Cir. 1998), the court held the claimed invention non-obvious, even though the combination of the references taught every element of the claimed invention, because no motivation to combine the references could be found. There, the claims included at least the following limitations: 1) a satellite communications system, and 2) an antennae system made up of a plurality of fan beams that elongate in the travel direction of the satellite. Rosen taught a satellite that used a plurality of fan beams with their long axes in an east-west direction. Ruddy taught fan beams sent from the ground station to the satellites with a long axis aligned with the axis of the satellite orbit. Both of these references dealt with similar technology areas, satellite communications with ground stations, but one of the primary differences relied by the court was that purpose of the Rouffet application was to minimize handovers between different satellites, whereas the prior art of Ruddy was not concerned with minimizing handovers, but with maintaining constant communication between the ground and a single satellite. As analogy to the present application, both Lohning et al. and Burger et al. teach the expression of antibodies or fragments, but there are significant differences in the approaches, as discussed above, and differences in the purposes of the two references. The purpose of Burger et al. was the selection of a cell line for production, and the purpose of Lohning et al. was the provision of a means of displaying antibodies on phage. Based upon these significant differences in both the disclosure and purposes of the references, just as in *In Re Rouffet*, no suggestion or motivation to combine the teachings exists. Additionally, in the present case, just as in *In Re Rouffet*, the Examiner does not explain what specific understanding or technological principle within the knowledge of one of ordinary skill in the art would have suggested the combination. Absent such an explanation, in *In Re Rouffet*, the court concluded that the Examiner selected the references with the assistance of hindsight, which is forbidden. *See also Al-Site Corp. v. VSI*

*Int'l Inc.*, 174 F.3d 1308 (Fed. Cir. 1999) (the level of skill in the art cannot be relied upon to provide the suggestion to combine references).

In addition, there is no reasonable expectation of success based upon Burger et al. that a library of tricistronic vectors would work in a phage display application. The Examiner states that Burger et al. may have disclosed that there were difficulties encountered, but Burger et al. was successful in the expression of three proteins. The successful expression of three known proteins having a known amino acid sequence, after considerable trial and error, within the context of cell line development is not enough to predict that a library of tricistronic vectors successfully displays billions of different antibodies in a phage display application. Burger et al. required repeated tri-cistronic transfections to produce four productive clones (6-1, 7-2, 7-4 and 9-1) and had the ability to test the quality and quantity of expression after the fact. This type of trial and error and quality assurance is in no way possible in a phage display application. In phage display, it is necessary that the library of vectors is able to express billions of different proteins predictably the first time without any quality assurance steps. Therefore, the use in stable cell line development shown by Burger et al., is in no way predictive of success in using a tricistronic vector in phage display, therefore, Applicant respectfully requests the Examiner to withdraw the rejection.

## **CONCLUSION**


In view of the foregoing amendments and arguments, Applicants respectfully submit that the application is in condition for allowance. Should the Examiner feel that there are any issues outstanding after consideration of this response, the Examiner is invited to contact the undersigned to expedite prosecution of the application.

The Commissioner is hereby authorized by this paper to charge any fees during the entire pendency of this application including fees due under 37 C.F.R. §§1.16 and 1.17 which may be required, including any required extension of time fees, or credit any overpayment to Deposit Account 50-4520. **This paragraph is intended to be a CONSTRUCTIVE PETITION FOR EXTENSION OF TIME in accordance with 37 C.F.R. §1.136(a)(3).**

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